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Translational Research**JORGE CARRASQUILLO:
IMAGES BECOME ACTION**

by Margaret Coulombe

The first FDA-approved radio-labeled antibody for imaging was born at NIH, and Jorge Carrasquillo was the sire of the radionuclide that was coupled to the antibody.

The antibody itself was discovered in Jeff Schlam's NCI Laboratory of Tumor Immunology and Biology. But it was from the ensuing collaborative clinical work between Schlam's and Carrasquillo's teams that there emerged in 1992 a new product to uncover metastatic colorectal and ovarian carcinoma (OncoScint, Cytogen Corp., Princeton, N.J.).

"It is fascinating to take something from its basic concept into the lab and then into the clinic," says Carrasquillo, deputy chief of Nuclear Medicine at the Clinical Center. "My main interest is translational research."



Margaret Coulombe
Jorge
Carrasquillo

And in his nearly two decades of research at NIH, where he came with his mentor in 1983 to establish a radioimmunodetection-radioimmuno-therapy program—in the Nuclear Medicine (NM) Department—Carrasquillo has been instrumental in the development of more than 40 clinical research protocols involving antibodies and radioisotopes.

As reflected in the partnership with Schlam, NCI scientists have been the

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Ruffin Named Director of New NIH Center**HEALTH DISPARITIES RESEARCH MOVES TO CENTER STAGE**

by Fran Pollner

TITLE I—IMPROVES MINORITY HEALTH THROUGH NIH: *The Health Care Fairness Act establishes a Center for Research on Minority Health [and Health Disparities] at NIH. The Center will oversee the development of an NIH-wide plan and budget for research on minority health. The Center will also award grants to institutions across the country that serve under-represented populations. These funds will be used to conduct research into the nature [and causes of] and remedies for health disparities, train minorities as biomedical research professionals, and improve infrastructure for conducting biomedical research. In addition, qualified health professionals who agree to engage in biomedical research on minority health will be eligible to receive \$35,000 from NIH to repay educational loans for each year they engage in such research.*

In May 2000, John Ruffin, director of the NIH Office of Research on Minority Health (ORMH) accompanied Surgeon General David Satcher to Capitol Hill, where they outlined NIH actions to research and eliminate health disparities among racial and ethnic groups; they endorsed legislation that would create a National Center on Minority Health and Health Disparities at NIH (see above "Title I" of the Health Care Fairness Act).

By year's end, the Center had sailed into existence through a bill handily passed by Congress and happily signed by the president on November 22; Ruffin, who had steered the ORMH since its inception in 1990, was named the new Center's director; and each NIH institute and center had crafted its own detailed "strategic plan" for targeting and eliminating health disparities related to its particular sphere of research. An NIH web site dedicated to health disparities went up in July:

<<http://healthdisparities.nih.gov>>.

Prelude to a Center

The health picture of minority populations in the United States, generally acknowledged as the basis for the country's low health status ranking among the industrialized nations, had prompted President Clinton in 1998 to launch the Racial and Ethnic Health Disparities Initiative, which set a national goal of eliminating these disparities by 2010. The legislation to establish the new NIH center was introduced the following year, and



John Ruffin

NIH responded to the initiative by establishing the trans-NIH Working Group on Health Disparities. Co-chaired by NIAID Director Anthony Fauci and NIH Acting Deputy Director Yvonne Maddox, the Working Group has aided the ICs in developing their strategic plans.

Center Projections

In signing the bill, President Clinton noted with satisfaction that it authorized

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PROTECTING THE INTEGRITY OF THE SCIENTIFIC ENTERPRISE



Michael Gottesman



Joan P. Schwartz

Scientists appreciate that the significance of data in the literature is always subject to interpretation and that disagreements may legitimately arise. Falsification of data, on the other hand, is not tolerated. Research integrity demands that certain standards be maintained in performance and presentation of research. Two new policies, one from the White House Office of Science and Technology Policy (OSTP) and the other from the Public Health Service Office of Research Integrity, recently codified these standards. The OSTP policy defines scientific misconduct and how to handle it. The PHS policy describes a training requirement for all PHS-supported researchers.

First, a bit of history. Over the past decade or so, several scientific misconduct cases have reached the halls of Congress, raising the consciousness of many Americans about the consequences of a scientist's committing scientific misconduct while doing research using public tax dollars.

As a result, the Commission on Research Integrity spent two years examining the problem and related issues and in 1995 made a series of recommendations to the HHS Secretary. Dr. Donna Shalala in turn established a committee to respond to those recommendations, and the OSTP convened the National Science and Technology Council, with representatives from all federal agencies that support research, to establish a definition of scientific misconduct that would apply government-wide. The final product was issued December 6, 2000, and is available at

[<http://www.ostp.gov/html/001207_3.html>](http://www.ostp.gov/html/001207_3.html).

It defines research misconduct clearly and succinctly as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research or in reporting research results. This will be the subject of a column in the next issue of the *Catalyst*.

Regarding the training requirement for all PHS-funded researchers, the final PHS policy on Instruction in the Responsible Conduct of Research (RCR) can be found at

[<http://ori.dhhs.gov/html/programs/finalpolicy.asp>](http://ori.dhhs.gov/html/programs/finalpolicy.asp)

and will affect all of us in the Intramural Research Program. The purposes of RCR training are to promote the responsible conduct of research and to discourage research misconduct and questionable

research practices. The PHS has defined the long-term goals of this training as:

- To increase knowledge of, and sensitivity to, issues surrounding the responsible conduct of research
- To improve the ability of participants to make ethical and legal choices in the face of conflicts involving scientific research
- To develop an appreciation for the range of accepted scientific practices for conducting research
- To provide information about the regulations, policies, statutes, and guidelines that govern the conduct of PHS-funded research
- To develop positive attitudes toward lifelong learning in matters involving the responsible conduct of research

Under the new policy, all research staff in the NIH IRP who have "direct and substantive involvement in proposing, performing, reviewing, or reporting research, or who receive research training" will be participating in RCR instruction. This includes senior investigators, tenure-track investigators, staff scientists and clinicians, research and clinical fellows, pre- and post-doctoral trainees, technicians, research nurses, and special volunteers or guest researchers involved in these activities.

Core areas defined for instruction in the PHS policy, and already covered in the "Guidelines to the Conduct of Research in the Intramural Program at the NIH"

(<http://www.nih.gov/campus/irnews/guidelines.htm>),

include data acquisition, management, sharing, and ownership; mentor and trainee responsibilities; publication practices and responsible authorship; peer review; collaborative science; research

misconduct; and conflict of interest and commitment. Two additional core areas—human subjects and research involving animals—are covered by other required courses at NIH and will be dealt with to the extent necessary.

The new policy requires one-time training in all of the above areas, to be completed by October 2003 and complemented with yearly follow-ups. The NIH Committee on Scientific Conduct and Ethics (CSCE) has proposed that the one-time training be met through a web-based computer module that will cover all the areas; it is to be taken by all cur-

**UNDER THE NEW
POLICY, ALL RESEARCH
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OR REPORTING RESEARCH,
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BE PARTICIPATING IN
[RESPONSIBLE CONDUCT
OF RESEARCH] INSTRUCTION.**

CATALYTIC REACTIONS

On Volunteer Activities

For seven to eight years now, I have thoroughly enjoyed the interactions with middle and high school students at the Montgomery (County) Area Science Fair. I see this as a chance to help promote the students' interest in science as well as being just plain fun and a chance to learn for me. I have also been pleased with the response in 1999 and 2000 when I was able to get the clinical fellows to pass around an e-mail announcement asking for volunteers for judges at the fair (held in March or April each year).

What was disappointing were the "rulings" from the Office of Education that encouraging science fair participation does not fall within its purview and from the Office of Science Education that it could not send out an NIH-wide e-mail invitation to judge in Montgomery County. While Dr. Fuchs [Bruce Fuchs, director, Office of Science Education] did offer to set up a website for judges similar to that for NIH speakers, he wanted information about ALL the science fairs in the area, not just [those of] NIH's host, Montgomery County—and this does not seem to be a good solution since the speaker website is so underutilized.

I would hope that the NIH administration could revisit what its role should be vis-a-vis local science fairs.

—Linda Silversmith, CC

—We do encourage people to support local science fairs, but we cannot show favoritism to one school system over another. One possibility is to use existing e-mail lists (such as the Fellows' list) to do this, rather than depend on a central distribution point.

—Michael Gottesman
Deputy Director for Intramural Research

I think that the editorial on "Volunteerism Among Scientists: Passing the Torch" [see *The NIH Catalyst*, September–October 2000, page 2] should serve as a reminder to all intramural scientists that they have an obligation to indeed "pass the torch" in whichever way suits their interests and time. I for one enjoyed immensely the time that I tutored students at a local "Saturday school." Unfortunately, the program had to rent school space and was unable to sustain itself for lack of funding. . . .

In reference to volunteer work with professional scientific societies, I have found the interpretation of ethics regulations at the NIH to be a significant hindrance in these activities. More specifically, I was informed a couple of years ago that if I served on a society's finance committee (a volunteer activity), EVERY activity with the society would be considered an "outside activity." This meant that editorial duties (a volunteer activity, and an important part of one's sci-

entific endeavors) could not be performed using government facilities (phones, e-mail). This would have made editorial work impossible.

I [support] removal of such irrational constraints on volunteerism, certainly where there is no remuneration or potential conflict of interest involved, and the activity is supported by the volunteer's supervisor.

—Raymond Mejia, NIDDK

—NIH employees are subject to the conflict of interest statutes and the Standards of Ethical Conduct for Employees of the Executive Branch. The regulations were written to provide a uniform legal framework in the federal workplace that would ensure the public's trust in the integrity of government decision making. Certain ethics rules must be followed by all government employees to prevent conflicts of interest—or even the appearance of a conflict of interest—between an employee's official duties and his or her outside activities.

Under the conflict of interest statutes, a conflict arises when an employee has a personal or imputed financial relationship with an outside organization and also deals with that organization as part of his or her official duties (for example, through a contract, a CRADA, or an official duty activity). Provided that an employee's supervisor makes a determination that a particular activity does not create a conflict, an employee is encouraged to participate in activities with outside organizations. Such participation may include membership in professional associations and societies and/or service on boards and committees of nonfederal organizations.

An employee may participate in activities of a nonfederal entity in one of two ways: as an official duty activity or as an outside activity. Official duties are extensions of regularly assigned duties, are performed during regular working hours, and require advance review and approval by the employee's manager. Examples include serving as a federal liaison to a professional organization, assisting other federal agencies, serving as an officer of a professional society, and serving as a peer reviewer of manuscripts for scientific journals. Conversely, consulting with industry for compensation or maintaining a private professional practice must be done as an outside activity. Taking financial responsibility for a professional society is also considered an outside activity because you have a legal obligation to act on behalf of the organization, which conflicts with your obligation to the federal government. Prior to engaging in any activity with an outside organization, an employee should consult with his or her supervisor, ethics counselor, or the NIH Ethics Office to ensure that the activity is legally appropriate and does not present any conflicts of interest.

—Donna Cencer, NIH Ethics Office
—Karen Dalheim, Office of General Counsel

rent staff before the deadline and incorporated into a web-based orientation package for all new staff.

For the yearly follow-ups, the CSCE strongly recommends the use of research ethics case discussions, led by a trained facilitator and given to groups of 20–30 people at a time. The Committee is developing a website that will contain sets of cases to be used for each topic and has decided that each year a theme will be chosen to be used NIH-wide. We are in the process of training investigators to serve as facilitators, who will ensure that everyone takes part in the discussion, that the key points are covered, and, most importantly, that the discussion is lively. This year (2001) the theme will be scientific misconduct. All staff will learn the new definition and the procedures for handling allegations of misconduct.

The ICs will have some flexibility in how they carry out the yearly training, but will be expected to adopt the theme chosen for that year. This mechanism will allow NIH to update staff on new policies relatively rapidly and inclusively. The CSCE has also been discussing the idea of developing a course in Research Ethics to be presented through the FAES Evening School, which would serve as a useful training tool for new facilitators. Any scientist interested in serving as a facilitator, or in helping to develop the FAES course, should contact his or her scientific director or CSCE member (for a list of IC representatives, see

<http://www1.od.nih.gov/oir/sourcebook/comm-adv/sci-conduct.htm>).

Many of you have already participated in these research ethics case discussions—several institutes have been conducting them over the last few years—so you already know that they can be intellectually stimulating and even fun. Over the next few months, your ICs will be acquainting you with the new PHS policy and its ramifications. We advise you to get involved in the process, and we ask you to share with us your ideas about how to improve the training experience.

—Michael Gottesman
Deputy Director for Intramural Research

—Joan P. Schwartz
Assistant Director, OIR

HEALTH DISPARITIES CENTER

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more than \$150 million to create a new center at NIH directly related to the initiative he'd announced two years before to counter racial and ethnic health disparities.

The legislation calls for an NIH-wide comprehensive plan and budget for the conduct and support of such research and requires the Center director to report annually to congressional committees, the HHS secretary, and the NIH director on relevant intramural and extramural activities. A Center advisory group will be created by HHS.

In general, the Center and, specifically, its head are directed and empowered to fund health-disparities investigators and designated "centers of excellence." Chosen institutions could receive funding to offer biomedical and behavioral research training to a significant number of members of minority or other health-disparity populations, as well as to update existing research facilities or construct new ones. Such funding would be limited to five years and subject to annual approval by the Center director.

The act also mandates an educational loan repayment program aimed at increasing both the amount of health-disparities research and the numbers of minority researchers: Investigators who agree to pursue minority-health or other health-disparities research can be awarded up to \$35,000 for each year of such research—and at least 50 percent of investigators awarded such contracts must be members of a health-disparity population.

The act enlists other agencies in the health-disparities mission as well: The Agency for Healthcare Research and Quality is required to identify disadvantaged populations in regard to the quality, outcome, cost, or use of health-care services—and to help develop strategies for change; the National Academy of Sciences is charged with conducting a comprehensive study of HHS systems and practices relating to the collection of data on race or ethnicity. ■



John Ruffin to steer a more buoyant ship

CC Department of Clinical Bioethics Forum**'UNDERSTANDING HEALTH DISPARITIES IN AMERICA' THROUGH THE LENS OF RACE, CULTURE, AND CLASS**

Kidney transplantation is a medical issue: A doctor diagnoses a condition that warrants a kidney transplant; the patient gets on the transplant recipient waiting list; with luck, the patient outlives the wait, and the surgery happens. Race, gender, culture, and socioeconomic class have nothing to do with the process—except that in real life, they do.

If you are African-American and have access to a certified clinical center that evaluates you for kidney transplant, and if you are then fortunate enough to be referred, the likelihood that you will receive a transplant is between 8.5 and 8.8 percent. The odds increase to 28–32 percent if you are white.

A rapidly expanding body of scientific and sociological research on health disparities is uncovering the fact that health care is not dispensed as impartially as one might expect. Last fall, the Department of Clinical Bioethics at the NIH Clinical Center provided a forum for the chorus of investigators at NIH and elsewhere who have been working to fulfill President Clinton's 1998 mandate to reduce health disparities in the United States. A forum held October 25 explored the underpinnings of medical inequities, attempting to differentiate disparities in health outcomes and availability of health-care services, with particular focus on renal diseases, cancer, and heart disease.

The kidney transplant issue was addressed by Arnold Epstein, of the Harvard School of Public Health. Inequity in this arena, he said, is the result of a cascade of disparate evaluation practices, some very subtle, that biases

access to transplant. Although doctors may attribute differences in treatment received by blacks and whites to "patient preferences," what data exist do not support that speculation. In fact, minorities receive less information, fewer referrals and spots on waiting lists, and more incomplete workups. "Once an incomplete workup is filed, if you are an African-American, you are again less likely to be referred and roughly four times less likely to receive a transplant," Epstein said.

"Overt discrimination is rare, but there is a pervasive pattern of whites getting more treatment than blacks. It is not an artifact of where people go to get treatment; it is an in-center effect," he noted. Another consequence of this differential treatment, however, is that whites are five times as likely to undergo inappropriate transplant procedures.

The Color of Cancer

"Every cancer has racial disparities, that is a fact we all know," observed Harold Freeman, associate director for reducing health disparities at NCI and chairperson of the President's Cancer Panel. He called race "the single most defining issue in the history of America" with significant repercussions in the realm of medical care. "But racial categories," he said, "were determined by racism. . . . and there is a need to disentangle the social meaning of race from biology."

Research has shown that African-American men have the highest incidence of cancer and the highest overall cancer mortality. Among women, African-Americans, Alaskan Natives, and whites have the highest cancer incidence, but African Americans and Alaskan Natives are more likely to die of the disease.

As a practitioner in Harlem, where 96 percent of his patients were black and 41 percent were poor, Freeman found that half of the African American women who presented with breast cancer were at stages that had gone beyond the reach of modern technology. "What is it," he asked, "that makes people come in so late, when the disease is incurable?"

Poverty and culture play heavy roles in cancer outcome. Survival is 10–15 percent lower among the poor. "There is a diminished access to health care, inadequate physical and social support systems, inadequate information, and riskier lifestyle, behavior, and attitudes." Culture, Freeman said, can modify the effects of poverty, as reflected in the social support systems found in poor Hispanic communities. And the nondrinking, nonsmoking culture of Seventh Day Adventists has been cred-



Harold Freeman



Arnold Epstein

by Margaret Coulombe

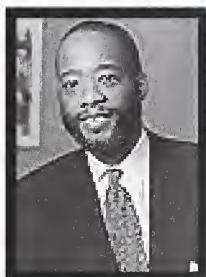
ited with that population's six-year cancer survival advantage.

"The effects of poverty translate into 10 years of life expectancy (loss) and 20 years of difference in disease development," said James House, director of the University of Michigan Survey Research Center. "There is a terrible accumulation of disadvantage across generations, but one can transcend early disadvantage and stop the process," he maintained, citing Social Security as an example of one program that has had a huge effect on health and mortality in older populations. He also credited the Civil Rights Movement with helping to narrow disparities, decrease infant mortality, and increase life expectancy overall.

Health Is Where the Home Is

Norman Anderson, the first director of the NIH Office of Behavioral and Social Sciences Research and now at the Harvard School of Public Health, arranged the causes of health disparities into three interactive categories requiring three different levels of analysis: social and environmental factors; behavioral and psychological factors; and biological pathways.

He, too, focused on the socioeconomic effectors of health. He cited William Wilson's "The Truly Disadvantaged," a study of residential segregation in Chicago and its effect on mortality. Published in 1987, the study showed that poor blacks—but not poor whites—overwhelmingly resided in neighborhoods where the majority of their neighbors were poor. Whites were more integrated with regard to socioeconomic status in housing, a finding with substantial health consequences because predominantly poor neighborhoods "were associated with all types of factors, all causes, that increase mortality; regardless of individual status (even if of higher income)." Anderson referenced another recent housing study that showed that realtors offered fewer rental units and housing options to blacks and more credit and favorable terms to whites when purchasing or renting homes.



Norman Anderson

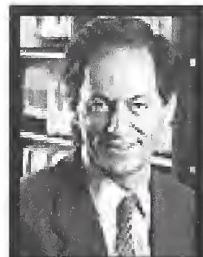
Job Perquisites

Michael Marmot's landmark "Whitehall Studies" followed the health of British civil servants of all grades over many years and found a correlation between longevity and health and one's grade of employment. "Non-smoking British administrators are nearly immortal, and that may account for some of our present problems," quipped Marmot, of University College, London.

The Whitehall II studies, begun in 1985, found that degree of control in one's job correlated inversely with disease risk. Low job control, for example, carried a 2.5-fold increase in coronary heart disease risk. Jobs with low effort and high reward were found to confer less disease risk than jobs with high effort and low reward.

Some studies suggest that money isn't everything; others, that it makes quite a difference. One of the former compared three nations with equivalent gross national product—South Africa, Hungary, and Costa Rica—and found that Costa Rica had half the infant mortality rate and at least seven more years of life expectancy than the other two. A money-is-the-root-of-disparities finding in another study showed that increased risk of later behavioral and cardiovascular problems in babies with low birth weight was ameliorated in those born to wealthier households.

And what at first glance in another British study appeared to be a pitfall of single-mom households compared with natural-parent or reconstituted two-parent households—a higher risk of behavioral problems in the children—on closer inspection turned out to revolve around economic status. This, Marmot noted, is a particularly interesting finding in a country with a national health system. Social and economic factors—Independent of health care access, which is universal in England—play a major role in health disparities. Indeed, 37 of 39 recommendations to address health disparities in the 1998 Acheson Report did not relate to health services (which are a given) but to such social programs as bus service for the elderly and tax adjustments for women and children. ■



Michael Marmot

ODP Seminar

To UNDO THE PAST

There are plenty of studies documenting that people are treated differently based on the color of their skin—and their gender—and that these treatment disparities exist regardless of socio-economic status," Stephen Thomas, director of the Center of Minority Health at the University of Pittsburgh Graduate School of Public Health, asserted at a seminar on eliminating health disparities, held last fall by the Office of Disease Prevention.

Breast cancer is more common in white women, but more likely to kill black women," he continued. "It is now cheaper to transplant a kidney than it is to do dialysis, but you will find more African-Americans on dialysis. Why is that? Why no donors? If you ask an African-American, that individual will say, 'I don't want to be teetering on life in an emergency room [and have someone take my organs]. If I sign that card, my organs will be more important than my life'."

Hesitation among minorities to seek medical help or participate in clinical research can be explained by one word—"Tuskegee"—a word that summons to mind differential treatment and a history of abuse, Thomas observed. "Anytime you are dealing with a vulnerable population, that is when issues of trust, justice, and race must be examined as factors. . . . 'Breakthroughs' in research mean nothing if they cannot be translated into improving the quality of life of the people who pay for the trials. We look for proof of institutional change," Thomas said, citing as a hopeful example at NIH the June 2000 appointment by NCI of Harold Freeman (see page 4) as associate director for reducing health disparities.

Freeman is the president, chief executive officer, and director of surgery at New York's North General Hospital. He was also the director of surgery at Harlem Hospital from 1974 to 1979.

—M.C.

NIAMS Conference**SCRATCHING THE SURFACE OF DISPARITIES:
DISEASES OF THE SKIN, JOINTS, MUSCLES, AND BONES**text and photos
by Margaret Coulombe**Multilayered Truths**

Beauty is not the only thing that is skin deep.

Speaking at a NIAMS-sponsored meeting here in December, Susan Taylor, director of The Skin of Color Center, at New York's St. Luke's-Roosevelt Hospital Center, addressed the lack of research in dermatological conditions in persons of color. Experimental bias based on race, she said, has left large gaps in dermatologic diagnosis and treatment among nonwhite populations. For instance, it is not clear why whites account for nearly 90 percent of office visits for common acne and for prescriptions filled for isoretinoic (Accutane), which has been found to be effective against acne regardless of skin color. Cultural habits of patients, lower rates of acne in blacks, and physician education could each play a role in these numbers, she observed, but there is a lack of sound scientific evidence to support an assumption that racial differences exist in the structure, function, and biology of skin and hair.

Closing such knowledge gaps underlies recent proposed and actual modifications of NHANES (National Health and Nutrition Examination Survey) protocols, according to Natalie Dupree, a NHANES researcher and Alexa Boer Kimball, a professor of dermatology and director of the Clinical Trials Unit at Stanford (Calif.) University Medical Center. Not only is NHANES now oversampling subgroup populations such as African-Americans and Hispanics but it is also studying the feasibility of including digital imaging of skin conditions to build up dermatologic databases and gather information in a statistically significant manner.

Conversely, African-Americans account for 90 percent of patients with keloids, a condition characterized by overproduction of dermal collagen during healing of a piercing wound, most commonly ear piercing. Sixty percent of patients have at least one close relative with keloids. Despite these statistics, the study of keloids is hampered by the usual stumbling blocks: a dearth of epidemiological data that would facilitate directed research at the cellular



Susan Taylor

Alexa Kimball (left) and
Natalie Dupree

and genetic levels, according to A. Paul Kelly, chief of dermatology at the King-Drew Medical Center in Los Angeles.

Lupus Erythematosus

Despite the fact that the incidence of systemic lupus erythematosus (SLE) is three to four times as high in African-American women as in white women, there is no firm understanding of what role, if any, race plays in its pathogenesis. Researchers presented an array of potential causes of SLE, underscoring the need for subgroup analysis.

Jane Salmon, professor of medicine at New York's Weill Medical College of Cornell/University Hospital for Special Surgery, looked at genetic variations in receptors for an immunoglobulin (Fc-R) and found that certain low-binding alleles of Fc-R were enriched in Hispanic and African-American patients with SLE. Genetic factors, she observed, may in part account for variation in SLE prevalence, clinical manifestation, course, and outcome among ethnic groups.

Patricia Fraser, of Harvard Medical School and Brigham and Women's Hospital, Boston, emphasized that behavioral, genetic, and environmental factors most likely combine to produce increased SLE risk. She pointed out that the risk for lupus is two to three times as high among smokers and/or those exposed to smoking in childhood. She also examined populations in four counties near Boston and found links between SLE incidence and environmental factors, such as living near petrochemicals and hazardous waste sites.

Glinda Cooper and her group at NIEHS found that breast feeding, which she noted is less common among African-American women, appears to confer some protection against SLE. The Environmental Diseases Study Group of the American College of Rheumatology documented ties between lupus and certain medications, heavy metals, chemicals, and other compounds. Elizabeth Karlson, of Harvard Medical School, reported links between socioeconomic

status and SLE morbidity and mortality, regardless of race. Overall, speakers agreed that understanding environmental determinants could help identify potentially modifiable psychosocial, behavioral, or clinical risks and possibly preclude induction of the disease in susceptible populations, regardless of ethnicity. Similarly, insight into the genetic basis of disease can offer clues to pathogenesis, provide predictors of disease severity, and perhaps suggest a means to develop possible cures.

Pain and Bias

Equal access to health care does not necessarily result in equal treatment or outcome.

In the session with the most heated discussions, speakers elaborated on the ways physician bias related to sex and ethnicity and patient mistrust can undermine disease management in such areas as osteoarthritis, joint replacement, and pain.



Patricia Fraser

Tim Carey, director of the Cecil Sheps Center for Health Services Research at the University of North Carolina, Chapel Hill, presented findings from studies undertaken with his colleague Joanne Garrett demonstrating a disconnect between patient status and physician interpretation. They found that lower back pain in blacks was accompanied by

higher pain scores and functional disability than in whites, but that practitioners believed that blacks actually experienced less severe pain than their white counterparts. These practitioners were less likely to consider disc disease or neurological treatment in their black patients. Radiographic and imaging studies were less frequently offered black patients, regardless of income, education, and insurance. Blacks were also less likely to be hospitalized or have surgery—despite similar care-seeking behavior—and over time had worsened functional status.

Additionally, according to Christopher Edwards, director of the Chronic Pain Management Program at Duke University Medical Center in Durham, N.C., Med-line and other searches in the area of pain retrieved only 49 articles among some 53,000 that contained references to black cohorts, most since 1996.

Patient preferences also contribute to



*Christopher
Edwards*

treatment disparities among white and minority populations. Dissatisfaction with conventional treatment, mistrust of the system, more faith in alternative approaches, and more self-reliance have been found to inform the health-care decisions of members of minority groups.

Augustine Escalante, of the University of Texas Health Science Center at San Antonio, pointed out that Hispanics have been found to underutilize hip replacement, compared with whites, independent of access to health care or insurance.

Kent Kwoh, director of clinical research in the Division of Rheumatology and Clinical Immunology at the University of Pittsburgh School of Medicine, found that minorities are half as likely to opt for joint replacement and more likely to use over-the-counter oils and lotions, copper bracelets, chiropractic, and prayer. And in a study of veterans with equal insurance and available counseling, African-Americans were found to expect more pain and less benefit from joint replacement than their white counterparts. Edwards suggested that some of these racial disparities might be explained by "John Henryism," a coping strategy among blacks based on the perception that "illness can be dealt with by hard work and confidence, rather than care seeking." Lawren Daltroy, associate director of the Robert B. Brigham Multipurpose Arthritis and Musculoskeletal Diseases Center at Brigham & Women's Hospital, pointed out that "in the absence of education, both African Americans and Hispanics have more nihilistic beliefs (about arthritis treatment)."

Learning Curve

The effect of education, outreach, and social support on patient health, pain management, care seeking, and treatment selection were attested to by individuals from health-education projects around the country, including the Los Angeles County Rheumatoid Arthritis Health Project, the Spanish Arthritis Self-Help Program (developed by Kate Lorig, director of the Stanford Patient Education Research Center, Stanford University School of Medicine), the New York State

Osteoporosis Prevention through Education Program, and the Michigan Arthritis Foundation's Arthritis Awareness-Urban Outreach program.

Lorig urged NIAMS to devote attention to practitioner education, the health effect of socio-economic status, and evidence-based clinical policy-making, as well as increased public education. She cited the NIH Academy (see "NIH Academy Up and Running," page 8) as a source of future investigators with the insight and training to reduce and ultimately eliminate health disparities.

Indeed, Academy students were vo-



Nicole Brown

cal and visible participants throughout the conference, and one, Nicole Brown, challenged each of the panelists to "develop your own NIH Academy program at your own institution."

Co-sponsors of this December 15-16 meeting were the NIH Offices of Research on Minority Health, Research on Women's Health, Disease Prevention, and Behavioral and Social Sciences Research, as well as the Centers for Disease Control and Prevention, the Arthritis Foundation, the American College of Rheumatology, American Academy of Orthopaedic Surgeons, and American Academy of Dermatology.

NIAMS Turns Policy into Practice

The NIAMS rheumatology research program now extends from the Clinical Center on the NIH campus to three clinic sites in Washington, D.C., where medically underserved people, including those who are homeless, can receive treatment for rheumatic diseases and, if warranted, can enroll in NIAMS clinical trials.

NIAMS' partner in this venture is Unity Health Care, Inc., a Washington-based nonprofit organization with community leaders in the African-American and Hispanic-Latino communities that has established the sites at which NIAMS will run its model community-based rheumatology clinic. This is the first tangible product of the NIAMS Health Partnership Program, an institute initiative designed to gain more insight into the reasons for health disparities, to treat and prevent complications and chronic disabilities associated with rheumatic diseases, to provide medical care for disproportionately affected members of minority groups and increase their participation in clinical trials, and to increase the number of underrepresented minority researchers at NIAMS and elsewhere.

Initially focused on arthritis, lupus, and other rheumatic diseases, the clinic will eventually treat patients with muscle, bone, and skin diseases as well. People can refer themselves or be referred by a physician from Unity Health Care or any other health-care organization. All care is free.

The main clinic houses rooms for examinations, physical and occupational therapy, health education programs, and a demonstration kitchen. Two outreach facilities, one at a homeless shelter, are staffed to screen and refer patients to the main clinic; transportation is provided.

There are three possible levels of care. The first level includes such services as physical and occupational therapy and recommendations regarding diet and exercise; initial screening is by nurse practitioners. If referral to a rheumatologist is needed, the second level of care comes into play and requires written informed consent. The patient would be enrolled in a natural history study and would receive standard medical care—including X-rays, blood tests, and other laboratory tests, which would be provided at the Clinical Center, along with transportation to and from NIH. The data amassed in this natural history study are expected to help explain the bases for health disparities. The third level of care would involve enrollment in clinical trials for patients whose condition warrants consideration for a particular experimental protocol; a separate consent form would be required in such cases.

Participation at all levels is voluntary, and patient requests for information sharing with other health professionals will be honored.

NIAMS expects to have a formal open house in the spring. ■

THE NIH ACADEMY: UP AND RUNNING— AND CHASING DOWN HEALTH DISPARITIES

by Margaret Coulombe

Only 17 months after its conception, the newest kid on the NIH block—the NIH Academy, a postbaccalaureate training program that emphasizes health disparities—materialized last fall with a pilot class of 10 students.

These 10, says Academy acting director LaShawn Drew, of the Office of Education, have a well-defined interest in health disparities; otherwise, the entry requirements are much the same as those for the postbac IRTA program (about 350 students—also a program developed to recruit a diverse cohort of college graduates with a budding interest in biomedical research; see *The NIH Catalyst*, January–February 1998, “Bac-Tracking” and “Postbac to the Future”). In fact, because interest in the Academy is so much higher than the number of currently available slots, Drew advises potential participants to apply to both programs.

Creating an NIH Academy was recommendation #1 of a committee formed in 1998 by then-NIH director Harold Varmus to devise ways to increase the numbers of minority investigators at NIH; the committee’s findings* were released in April 1999; and an NIH Academy Working Group was formed by Michael Gottesman, Deputy Director for Intramural Research, the following month. Co-chaired by Arlyn Garcia-Perez (OIR and NHLBI) and Levon Parker (NINDS), the working group produced the blueprint for the new entity in a little under one year. Drew took the helm of the NIH Academy in April 2000, just days after the admission application was posted on its website:

<<http://www.training.nih.gov>>.

By June 19th, more than 140 students had applied for the 10 places. With the application period for the next class (2001–2002) running from mid-November 2000 until April 2, 2001, the numbers seeking admission could triple, Drew observes.

The Academy has gathered 45 precep-

tors—consenting tenure-track and senior investigators recommended by the scientific directors at each institute for their research and mentoring excellence. Matching preceptor to trainee proceeds along lines of mutual selection. The preceptors and the trainees basically “match themselves,” Drew says.

In the first round, once the top 10 applicants had been selected, Drew gave their applications, including their cover letters, to the 25 or so then-available

the provided housing (unlike the IRTA program, the NIH Academy is a residential program and has secured a small group of apartments in nearby Bethesda), and initiating the process of applying to a graduate or medical school.

Each institute with an academician provides the funding: a \$21,000 stipend, increased to subsidize the required housing, and support to attend one scientific meeting a year (whether the student presents or not) and to cover any FAES courses the mentor deems necessary. The Academy’s research-based training balances seminars on topics related to health disparities with skills development and general knowledge workshops. Students learn how to deliver oral and poster presentations, analyze journal articles critically, and understand epidemiological studies and data handling, as well as how to maximize opportunities to get into graduate schools and to fund or repay the tuition for them. One night a week, research is presented—either by a preceptor, a student, or an invited speaker. Not infrequently, the topic involves health-disparities research.

Also as part of the curriculum, each student submits a proposal that allows the class to see the effect of health disparities on people and communities—to see, as Drew puts it, “the faces of the community that they will be serving. . . . How are you going to be a biomedical researcher if you aren’t going to see the faces of the people suffering from health disparities? You need to see the human side,” Drew says.

This year’s proposals run from visits to clinics, like the Whitman Walker Clinic, which serves Washington’s gay and lesbian community and has been in the forefront of HIV and AIDS care, to training in cardiopulmonary resuscitation. Field trips are planned to two Washington-based projects—La Clínica Del Pueblo, a Hispanic health clinic, and the Barney Neighborhood House, which provides free meals, medical services, and other assistance primarily to poor, elderly African-Americans.

Academy students will also be work-



Pioneer Class of the NIH Academy: (bottom, left to right) Vanessa Shaw, Nicole Brown, Carrie Viens, José Cordero; (middle, left to right) Acting Director LaShawn Drew, Tarice Barnes, Jessica Diggs, Sara Angleman, Working Group Co-chair Arlyn Garcia-Perez; (top, left to right) Mac Baker, Quetzalsol Lopez-Chacon, Juan Marin

preceptors. Each preceptor selected, in priority order, the five individuals they thought would fit best in their labs.

Drew then presented to the trainees a list of all the preceptors who’d selected them—and in what order—and advised them to set up an interview with each potential mentor. Some of the interviews were “eye to eye,” she recalls; others were by phone and e-mail. It was then the students’ responsibility to choose their mentors and to inform Drew of their selections by a certain date.

Finally, each student signed a formal agreement committing to such things as working in a particular lab with a particular preceptor for the year, living in

* The Report and Recommendations of the Committee for Recruitment of a Diverse Workforce in Medical Research, known as the Slavkin Report, after committee chair Harold Slavkin, former NIDCR director.

ing in a Washington-based community health center for underserved and homeless persons with rheumatic diseases developed by NIAMS (see "NIAMS Turns Policy into Practice," page 7), where they will assist in patient health education and information dissemination.

In her own travels to spread the word about the NIH Academy to potential students from diverse backgrounds, Drew has encountered obstacles to seeking such training in different cultural and economic settings. Not having enough money for both food and higher education is one barrier; being afraid of failure in striking out on a novel career path is another.

The NIH Academy is not the only NIH program to address health disparities, Drew notes. Every institute has a "strategic plan" to address the issue (see "Health Disparities Research Moves to Center Stage," page 1), and health disparities are becoming a big blip on the national radar screen. The NIH Academy Working Group, Drew notes, anticipates that "eventually there will be 'NIH Academies' in different colleges and universities" around the country. She also envisions partnerships fostered by the NIH Graduate Partnerships Program (GPP). She and GPP Director Mary DeLong have discussed forging a combined Master's in Public Health Program with several universities.

"A student comes into the Academy for one year, but that can be extended to two," she remarks. "Three students told me from the outset that they wish to extend their time here, so wouldn't it be nice if during that two-year period they could work toward a Master's degree? The degree could be a Master's in Public Health with an emphasis or concentration on Health Disparities, or it could be a Master's in Health Disparities. It would depend on the partnering school."

Such plans are tentative, but Drew's advice to current and potential Academy students is not: "If you really have a desire, if that is what you know you are supposed to do, just settle it in your heart that that is what you *will* do." What she will do, she says, is "help you get there." ■

Some Destinations

Sol Lopez-Chacon, accepted to Stanford Medical School in 2000, deferred until 2001 in order to gain more NIH Academy experience. Jessica Diggs has been accepted into medical school at Case Western Reserve University in Cleveland. Others have been called in for interviews elsewhere, and still more plan on taking April 2001 MCAT and GRE tests for the 2002 entering class. ■

Yesterday's Student, Today's Mentor

LaShawn Drew, acting director of the NIH Academy, is herself an example of how early involvement at NIH can influence one's life commitments. A graduate of Atlanta's Spelman College, she came to work as a research assistant with Ana Chepelinsky at NEI and was drawn to the world of biomedical research.

In 1993, her bachelor of science degree in hand, she became a graduate student at Howard University in Washington, D.C., where she did basic research in sickle cell anemia.

A chance meeting with Rose Pruitt (then EEO officer for NIDDK) led to her entry into the NIH lab of one of the world's foremost researchers in the hemoglobinopathies—Griffin Rodgers, chief of the Molecular and Clinical Hematology Branch



Fran Pollner
LaShawn Drew

and now deputy director, NIDDK. She became his summer student in 1995. A liaison between Howard University, NIH, and Rodgers enabled Drew to complete her dissertation research and thesis in Rodgers' lab, where, after she received her Ph.D. in 1998, she stayed on as a postdoc until her appointment to the NIH Academy in April 2000.

During her graduate studies, she also taught courses through FAES at NIH and at local colleges and even devised course curricula for her church.

"Good mentorship taught me, now that I am in this position, how I can mentor others. One of the biggest lessons: Never tell someone that they cannot do something. You show them ways to better themselves—to get to the next step." ■

Today's Student, Tomorrow's Mentor

José Cordero is one of the 10 examples of dynamism that the NIH Academy is ushering into the world of health-disparities research and leadership. A graduate of the class of 2000 at the University of Tampa (Florida), he came to NIH with a degree in biochemistry and an attitude. "I want to open doors, to make a difference. I don't know if I can, but I have it inside of me to want to, and I think that is all you really need."

In the lab of Juan Rivera, head of the Signal Transduction Group in the NIAMS Arthritis and Rheumatism Branch, Cordero does asthma research. Rivera, he says, offered him a position of independence and one in which his research could have the greatest influence on health disparities. "He said two things that were very important to me," Cordero recalls: "that he would expect of me as much as he expects of himself and that he saw science as a way of life, something you want to wake up to every morning."

"I feel lucky to be in that lab."

Cordero is fueled with an "internal urgency and a sense of purpose" about do-

ing bench research, working with people, and saving lives. "I like the idea of answering questions at a very fundamental level and showing people that this molecule and this pathway can impact either deleteriously or beneficially mechanisms that occur in their bodies. It is so beautiful; it can be so small and have such an impact."

Cordero's aiming to obtain M.D. and Ph.D. degrees and finds appealing the prospect of working in pediatric neurology. He plans on spending two years at the NIH Academy.

"There is something special about the whole atmosphere here (at NIH). You get that feeling of purpose here. I count my blessings." ■



Fran Pollner
José Cordero

CARRASQUILLO: IMAGES BECOME ACTION

continued from page 1

main co-investigators in these projects and have served as the physicians to the patients enrolled in CC clinical trials in this "brand new area of research"—nuclear medicine in diagnosis and therapy.

Carrasquillo's radioimmunotherapy brewery resides at the Building 21 Nuclear Pharmacy, where NM chemist Chang Paik performs the preliminary labeling and testing of research reagents destined for clinical trials. Carrasquillo and his team also occupy a 4th floor lab in Building 10, where they assay products to ensure their quality and function and perform pharmacokinetic analyses on patient samples.

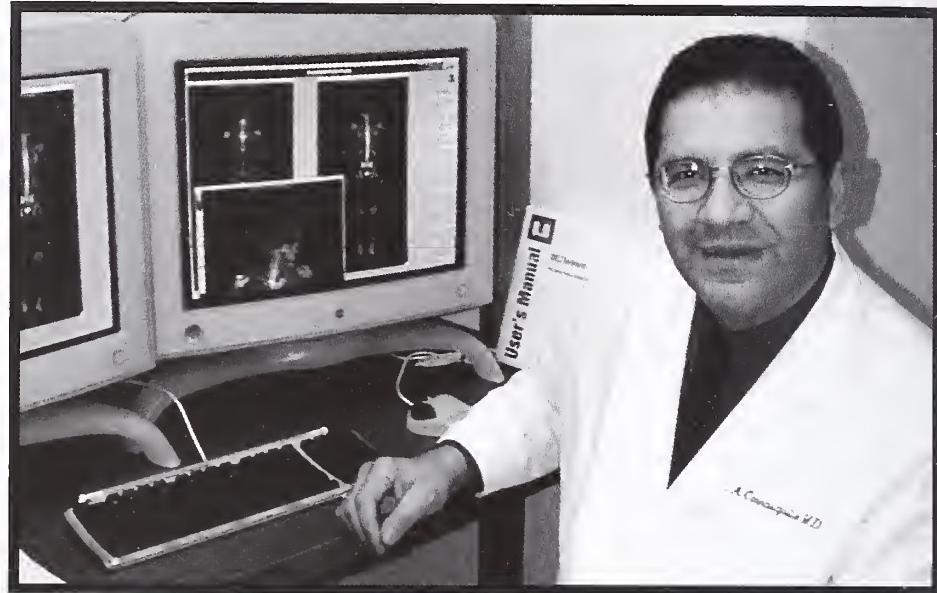
To support an IND (investigational new drug) submission to the FDA, the NM team typically characterizes and tests the desired radiolabeled antibody both in vitro and in animals. Then Phase I clinical trials are designed and implemented with one or more (usually) NCI collaborators.

During a trial, the NM team takes serial blood samples, urine specimens, and often bone marrow or tumor biopsies to evaluate the distribution of the monoclonal antibody in the body. The pharmacokinetic data, together with the imaging data, are used to calculate dosimetry and help guide changes in protocol.

Home Runs

With Tom Waldmann, chief of the NCI Metabolism Branch, the NM team has performed preclinical evaluations and clinical analyses of pharmacokinetics and dosimetry of anti-Tac monoclonals (directed against the IL-2R α receptor) in patients with adult T-cell leukemia [Treatment of Tac-Expressing Cutaneous T-Cell Lymphoma and Adult T-Cell Leukemia with Yttrium-90 Radiolabeled Anti-Tac]. Initial results, including two complete remissions, were promising. Ongoing clinical trials are focusing on using humanized anti-Tac for therapy.

Carrasquillo points to Phase I and II trials as the most fulfilling segment of his work. "The most satisfying part is getting something into the clinic that has potential to help patients. Anti-Tac [see "Anti-Tac Takes Off in Three Directions," *The NIH Catalyst*, March–April 1998, page 1] is an example of a successful outcome, with good patient responses. Unfortunately, it's not often that you hit



Margaret Coulombe

Jorge Carrasquillo

As a resident in nuclear cardiology at the University of Seattle, Carrasquillo anticipated a conventional clinical practice, but his work with Steve Larson, then chief of nuclear medicine at the Seattle Veterans Affairs Hospital and a pioneer in radiolabeled antibody research, changed his outlook. Instead, he came with Larson to NIH in 1983 to establish a program in radioimmundetection and radioimmunotherapy. Carrasquillo became the head of the Nuclear Medicine Antibody Program in 1985. He is deputy chief and one of five nuclear medicine physicians in the CC Nuclear Medicine Department.

a home run like that," he adds. However, Carrasquillo also has some runs batted in—end products in which he clearly had a direct influence if not a direct hand.

He points to two radiolabeled immunotherapy products now nearing the market as treatments for non-Hodgkin's lymphoma—Bexxar™ (Coulter Corporation, Miami, Fla.) and Zevalin™ (IDEC Pharmaceuticals Corporation, San Diego, Calif.). The former couples iodine-131 to a monoclonal antibody, and the latter links an antibody to yttrium-90. "At NIH," he notes, "we performed the first successful studies targeting lymphomas with indium-labeled antibodies. It's building this kind of knowledge base that allows development of such products and reagents by others."

Loaded Bases

Collaborations with Ira Pastan, chief of the Laboratory of Molecular Biology, NCI, and his team have been particularly fruitful. One study aims to "develop chemical methods to radiolabel monoclonal antibodies and fragments to con-

struct scintigraphic imaging agents that detect hematologic malignancies that express IL-2 α receptors." The goal is to label "genetically synthesized single-chain disulfide stabilized variable region fragments (scdsFv) of anti-Tac with Tc-99m for tumor imaging."

"In this investigation, we realized that because of their small size, scdsFv fragments had high renal uptake. This led us to a different line of research that resulted in animal studies that suggested optimal ways to block this uptake by using amino acid infusions or by chemically modifying the Fv fragments," Carrasquillo recalls. The two teams also worked together on preclinical studies with indium-111-radiolabeled immuno-toxins.

A collaboration with Pastan in progress since 1992 involves B3 antibody, which Pastan developed and characterized and which Pastan and Carrasquillo have been exploring as the basis for radioimmunotherapy in colon and breast cancer. B3, says Carrasquillo, is an "interesting" antibody that recognizes Lewis Y antigen, which is ex-

pressed in high concentrations in various adenocarcinomas.

"Using a xenograft tumor model, my group demonstrated excellent targeting of radiolabeled B3 monoclonal antibody," he says. The finding warranted the filing of an IND with the Food and Drug Administration and resulted in approval of a Phase I clinical trial conducted by Pastan and his NCI colleague Lee Pai.

A follow-up trial, in collaboration with Pai and NCI's Michael Bishop, is testing a higher radiation dosage with bone marrow support and is ongoing. Carrasquillo continues to design improvements—such as pretargeting—to incorporate into future clinical trials.

In 1998, Carrasquillo and Pastan applied for and received a Bench to Bedside Award to study "pretargeting" in the treatment of epithelial cancers with radiolabeled monoclonal B3 antibody.

In conventional antibody therapy, radioactive material is coupled to the antibody at the outset. But because most antibodies are fairly large and circulate slowly, surrounding tissues and organs may be damaged by the time the radionuclide finds its mark. The pretargeting strategy investigated by Carrasquillo separates the tumor targeting from the radionuclide delivery.

To do this, the antibody is coupled to the nonradioactive "sidearm" streptavidin, a reagent that recognizes biotin—the small, speedy molecule to which the radionuclide is attached. The antibody package is delivered first and can take its time localizing to the tumor without inflicting damage on surrounding tissues and organs; once tumor localization is achieved, the radionuclide is sped on its way to the tumor by its biotin chauffeur.

"If you attach the radioactivity to biotin, a relatively small molecule, it will get out of the circulation quickly and bind to the streptavidin to which the antibody is attached. What does not attach to the target antibody is quickly eliminated from the system," Carrasquillo explains, noting that the work could not have been done without the Bench to Bedside Award, an award established in 1998 by the NIH Clinical Research Revitalization Committee to encourage intramural collaboration between clinical and basic researchers at NIH.

Carrasquillo is now studying the

pretargeting approach in the xenograft setting, in which animal models have yielded results promising enough to pursue reagents for clinical studies, he says.

PET Projects

Carrasquillo is particularly enthusiastic about ways to capitalize on the CC's positron emission tomography (PET) facility, under the direction of Bill Eckelman, to enhance current options in tumor diagnosis and cancer therapy monitoring.

Radioactive materials that give off a single gamma ray when they decay are those traditionally used in nuclear medicine, he notes. Those called positron emitters, on the other hand, release a positively charged electron when they decay, which, in turn, gives off two 511KeV gamma rays, 180 degrees apart. The PET scanner can detect these gamma rays and make exquisite images of their distribution, Carrasquillo says, enabling researchers to "label biological compounds and trace physiologic events to answer clinical questions."

"Very exciting."

Among these positron emitters are carbon-11, oxygen-15, nitrogen-13, and fluorine-18.

Carrasquillo describes several ongoing PET protocols that rely on trace amounts of these positron emitters to measure blood flow and blood volume. Tiny amounts, he notes, citing the "tracer prin-

ciple," do not perturb the system but allow tracing of the physiologic processes of interest.

Blood flow, blood volume, and glucose metabolism in tumors are the measures of interest in studies undertaken in collaboration with Steve Libutti (NCI) and Steve Bacharach (Nuclear Medicine) to evaluate the effects of anti-angiogenic agents. "Patients are being treated with different antiangiogenic agents, such as anti-VEGF [vascular endothelial growth factor] on various NIH protocols," Carrasquillo elaborates. Using PET imaging techniques, he says, the investigators can assess whether these reagents result in relevant changes in blood flow, blood volume, or glucose metabolism. "PET thus may serve as a surrogate marker of what is happening at the tumor level."

Most recently, Carrasquillo has applied his PET activities to collaborative work with NIAID's Anthony Fauci and Douglas Brust using fluorodeoxyglucose (FDG) as a measure of glucose metabolism and, by extension, a possible indirect marker of sites of HIV infection and active viral replication. The research applies the tumor-imaging properties of the positron emitter fluorine-18 to the search for HIV reservoirs. The radiolabeled FDG reagent is taken up by cells with high glucose metabolism and becomes trapped inside them, resulting in an unusually high signal that flags the possibility of viral activity. ■

Balaban Elected President

Robert Balaban, scientific director of the Laboratory Research Program and chief of the Laboratory of Cardiac Energetics, NHLBI, has been elected president of the Society for Cardiovascular Magnetic Resonance (SCMR). The SCMR is a rapidly growing international society, with a current membership of about 600, that focuses on the cardiovascular applications of magnetic resonance imaging and spectroscopy.

Over the last decade, Balaban has been developing the NHLBI research and clinical program in cardiovascular MR, as well as overseeing the joint NIH-Suburban Hospital emergency room MRI program, together with Steven Warach, NINDS, and Andrew Arai, NHLBI (see "New Clinical Research Plans Leap Space and Specialty Barriers," *The NIH Catalyst*, January–February 1999, page 1). Balaban also serves as the chair of the steering committee for the In Vivo NMR Center on campus. ■



Bob Balaban

RECENTLY TENURED

Joshua Farber received his M.D. degree from the Johns Hopkins University School of Medicine, Baltimore, in 1977 and completed residency and fellowship training in infectious diseases at the Johns Hopkins Hospital. He did postdoctoral work in the laboratories of Earl Stadtman (Laboratory of Biochemistry, NHLBI) and Daniel Nathans (Department of Molecular Biology and Genetics, Johns Hopkins University School of Medicine). He joined NIH in 1993 and is now a senior investigator in the NIAID Laboratory of Clinical Investigation.

My clinical training in infectious diseases and my basic science training in molecular biology led me to search for novel genes induced in macrophages in response to factors produced by activated T cells. I presumed that such genes would encode proteins important in defense against infection and inflammation, and I was particularly interested in identifying secreted proteins because either the proteins themselves or small-molecule agonists or antagonists of their receptors might be useful therapeutically. In my screening using material made from mouse macrophages, I discovered genes encoding two proteins, Mig and CRG-2/IP-10, that belong to a family of secreted proteins now known as chemokines. These discoveries served as the starting point for my work at NIH.

The chemokines are now recognized as a family of more than 40 chemotactic cytokines that are of critical importance in regulating the trafficking of leukocytes throughout the body as part of leukocyte development and differentiation, homeostasis, and host defense. Chemokines signal through seven transmembrane-domain G-protein-coupled receptors, of which 18 have been identified in humans. Signals produced by these receptors are necessary for the activation of integrins on the surfaces of leukocytes, which is in turn required for white-cell adherence to endothelium and egress from the vasculature into lymphoid organs and tissue. These signals are also presumed to be important for the positioning of leukocytes within tissues after leaving the circulation.

Mig, IP-10, and a third chemokine, ITAC, were found to share a receptor,



Joshua Farber

CXCR3. Besides their roles in leukocyte physiology, chemokine receptors—particularly CCR5 and CXCR4—were found to function with CD4 as obligatory co-receptors for the entry of HIV and SIVs into cells, discoveries that provided major insights in HIV and SIV biology and disease and have created the possibility for new therapeutics.

In characterizing the Mig protein, members of my laboratory found that this chemokine targeted T cells and, in particular, T cells that had been recently activated. Analysis of experimental infections in mice revealed widespread induction of Mig and CRG-2/IP-10 in response to production of IFN γ . We presumed that Mig and CRG-2/IP-10 were important for recruiting activated T cells as well as other CXCR3-expressing cells, such as natural killer cells, to peripheral tissues for host defense. While experiments in our and other laboratories have

supported this presumption, experiments with Mig knockout mice that we created revealed an unexpected role for Mig in the optimal production of antibody against a bacterial pathogen. These and other recent studies of ours using human tonsils have suggested that a pro-inflammatory chemokine such as Mig may have a role within lymphoid organs in optimizing interactions among T cells, B cells, and dendritic cells.

Besides our work on chemokines, my laboratory also discovered two chemokine receptors expressed on lymphocytes that are now known as CCR6 and CXCR6, and we cloned and characterized two forms of a third lymphocyte chemokine receptor, CCR9. We found that CCR6—the receptor for Mip-3 α , a chemokine induced by pro-inflammatory cytokines at epithelial surfaces—was expressed on subsets of memory CD4 $^+$ T cells that home in on the skin and the intestine. Of particular interest, CCR6 was also expressed on both naïve and memory B cells, and activation of B cells through antigen receptors led to a significant increase in receptor activity without changing the number of receptors per cell. Together with data of ours for other chemokine receptors on T cells, this observation suggests novel mechanisms for regulating chemokine receptor expression on activated lymphocytes.

Understanding these mechanisms is one focus of my laboratory's current work. We reported that CCR9 is a receptor for TECK, a chemokine expressed constitutively by the epithelia of the thymus and small intestine. CCR9 is expressed on thymocytes and specifically on the subsets of memory T cells of the intestine. We found that alternative splicing of the CCR9 mRNA led to two forms that vary at their NH-termini, and that these forms, CCR9A and CCR9B, respond to different concentrations of TECK. This represents a new way of extending the range of concentrations over which a cell can respond to a chemokine ligand.

Finally, my laboratory has worked on understanding the role of the chemokine system in AIDS. We discovered a receptor that we named STRL33, now called CXCR6, that, together with our collaborators in NIAID and the FDA, we found functioned along with CD4 as a co-receptor for diverse strains of HIV and SIV. And we collaborated on the first studies to show that envelope glycoproteins of HIV and SIV can signal through the primary HIV and SIV co-receptor, CCR5.

Taken together, our studies and those of many other labs suggest that particular chemokine receptors function to direct the migration of specific lymphocyte subsets, defined by the cells' states of development, activation, and differentiation, as well as the compartments onto which the cells home. We seek more detailed understanding of the roles of the individual chemokine receptor-ligand groups in host defense, immunopathology, and AIDS in order to reveal how the chemokine system functions as a whole in lymphocyte biology. We expect that by manipulating the system—such as by using chemokine receptor antagonists now under development—we will better understand how to treat both AIDS and immune-mediated disease.

Fellows Career Workshops

Where: Building 10, Lipsitt

Time: 9:30 a.m.

1) Feb. 8, 2001: Patent Law

Kathleen Kerr, U.S. Patent Office

Grant Reed, attorney

Maria Freire, OTT, NIH

2) Feb. 22, 2001: NIH Administration

LaShawn Drew, NIH Academy

Sharon Gordon, OE, NIDCR

Reception to follow events.

For more info: <aains@box-a.nih.gov>

Ashok Kulkarni received his Ph.D. from the Maharaja Sayajirao University of Baroda, India, in 1980 and did postdoctoral work at Columbia University in New York and in the Developmental and Metabolic Neurology Branch, NINDS, before joining NIDCR in 1995. He is now a senior investigator and head of the Functional Genomics Unit, NIDCR, and director of the NIDCR Gene Targeting Facility.

My interest is in functional genomics as it relates to *in vivo* gene function, with a focus on candidate genes in development and disease. In my early work, I generated and characterized transforming growth factor- β 1 (TGF- β 1) knockout mice. These mice were shown to develop multifocal inflammation with similarities to human autoimmune disorders. Further analysis of these mice revealed critical roles of TGF- β 1 in embryonic development, hematopoiesis, inflammation, tooth mineralization, and carcinogenesis.

My lab used gene targeting to generate a much-needed animal model for Fabry disease, a painful and fatal X-linked lipid-storage disease. We disrupted the α -galactosidase A gene in mouse embryonic stem cells to generate a line deficient in this enzyme. These mice develop subclinical symptoms similar to those in Fabry disease patients. With collaborators, we demonstrated the effectiveness of bone marrow transplantation, gene therapy, and lipid deprivation to ameliorate metabolic defects in Fabry mice. We are continuing work with this mouse model to develop therapeutic approaches to Fabry disease.

Another focus of my research is molecular mechanisms underlying neuronal phosphorylation and its role in neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and Alzheimer's disease. We first generated cyclin-dependent kinase 5 (Cdk5) null mice. These mice show abnormal neuronal migration, cerebellar defoliation, and abnormal motor neurons. Although this mouse model revealed unique roles of Cdk5 in neuronal migration, it was of limited value in studying the aging nervous system because of its neonatal fatality. To circumvent this problem, we

developed Cdk5 conditional knockout mice in which Cdk5 is disrupted after neuronal migration is complete. These mice display locomotor and postural abnormalities along with neuromuscular defects that mimic some of the symptoms found in ALS patients.

We have also used gene targeting to generate mouse models for hereditary dental disorders, such as amelogenesis imperfecta (AI) and dentinogenesis imperfecta (DGI). Mice bearing a targeted mutation in the amelogenin gene, which is implicated in AI, have discolored and disfigured teeth. These defects are similar to those seen in AI patients, and these mice will be valuable for understanding the role of amelogenin in tooth development and designing treatments for this disorder.

We have also targeted overexpression of TGF- β 1 to teeth using a tooth-specific promoter. Mice overexpressing TGF- β 1 in teeth develop discolored and fractured teeth, which resemble the tooth phenotype seen in DGI. We are currently analyzing the role of TGF- β 1 in tooth development and disease using proteomics and genomics.

Our overall goal is to use functional genomics to identify specific roles of genes in the molecular processes that underlie development and disease. Doing so will also help us unravel functions of the numerous genes being identified in human and mouse genome studies.

Leonid Margolis received his Ph.D. from Moscow State University, where he also earned an advanced doctoral degree in 1985. He progressed through the academic ranks there to full professor and lab chief. With the beginning of "perestroika" and collapse of the Soviet Union, he worked as a visiting professor at University College, London, and Johns Hopkins University in Baltimore. In 1994, he became a Fogarty Scholar-in-Residence at NIH. He joined NICHD's Laboratory of Cellular and Molecular Biophysics in 1995, where he now heads the Intercellular Interactions Section; he is also deputy director of the NASA/NIH



Ashok Kulkarni

Center for Three-Dimensional Tissue Culture

In a broad sense, I would like to understand the mechanisms of normal and pathological cell behavior in a native microenvironment of real tissue *in vitro*. The biology of any given cell depends on a complex system of local contacts with cellular and noncellular structures within the tissue.

Meanwhile, most of our knowledge in cell biology comes from experiments on isolated cells that do not adequately represent the complexity of cell-cell interaction. Specifically, my current interest is to understand tissue HIV pathogenesis.

Critical events in HIV disease occur in lymphoid tissue, where HIV infects cells via surface molecules, CD4, and one of the co-receptors, CXCR4 or CCR5. Infection leads to CD4 $^{+}$ T lymphocyte loss, deterioration of cell-cell interactions, and immunodeficiency. To study HIV tissue pathogenesis, we developed a new system of human lymphoid tissue infected with HIV-1 under controlled conditions *ex vivo*. The goal was to delineate the role of viral co-receptors in HIV pathogenesis.

There are three important unanswered questions I want to answer: 1) why HIV infection is transmitted by viruses using the CCR5 co-receptor, 2) why later in the course of HIV disease CXCR4-utilizing variants often evolve, and 3) why this switch of "co-receptor tropism" coincides with rapid CD4 $^{+}$ T cell depletion and development of immunodeficiency.

Over the last few years, together with members of my unit—in particular, Jean-Charles Grivel, Svetlana Glushakova, and Wendy Fitzgerald—and encouraged by LCMB Chief Joshua Zimmerberg, we have focused on answering the last of these three questions. Using chimeric isogenic viruses that differ only by the sequences in the viral envelope protein that determine co-receptor recognition, we demonstrated that HIV-1's use of CXCR4 is sufficient to induce severe T lymphocyte depletion.

We delineated the mechanism of this phenomenon, explaining why CCR5-utilizing HIV-1 variants deplete far fewer CD4 $^{+}$ T lymphocytes than CXCR4-utiliz-



Leonid Margolis

RECENTLY TENURED

ing viruses—namely, because fewer T lymphocytes express CCR5 than CXCR4. Surprisingly, some of the “dual-tropic” viruses that in transfected cell lines recognize both co-receptors (and which comprise the majority of HIV isolates), in human lymphoid tissue use only one co-receptor. In this setting again, CXCR4 usage is associated with severe CD4⁺ T lymphocyte depletion because its prevalence makes the cells cognate targets for these viruses.

Furthermore, we found that ex vivo human lymphoid tissue retains immune function and responds to antigen challenge by producing specific antibodies. CXCR4- but not CCR5-utilizing HIV strains suppress this immune function in ex vivo tissues. We are now trying to understand the mechanism for such a dramatically different immune response in tissues infected with HIV-1 that differ only in co-receptor tropism.

I am now focusing more on the first two of our main questions regarding HIV transmission and the co-receptor switch. I think they should be addressed at the highest level of tissue complexity, involving cell-cell interactions and cell trafficking. I expect to use the NASA bioreactor—available through the NICHD-based NASA/NIH Center for Three-Dimensional Tissue Culture—to try to combine various human tissues with lymph to create a multicompartment “artificial patient.” In this system, we will test various hypotheses regarding virus transmission as well as various antiviral drugs and possibly vaccines.

My dream is to develop new techniques to monitor the interactions of a cell—how it establishes and disrupts cell-cell contacts and changes its metabolism in response.

Although my current focus is predominantly on HIV, several ongoing projects address mechanisms of tissue pathogenesis by other human pathogens, such as parasites, bacteria, and other viruses. I think that our studies are important for developing new ways to understand, prevent, and treat the diseases caused by these agents, as well as for development of new diagnostics. I believe that in the 21st century, “biology” will increasingly become “tissue biology,” emphasizing the cell—not as a separate entity, but as an element of a multicellular structure. My research is aimed at this goal.

Paul Roche received his Ph.D. from Duke University in Durham, N.C., in 1988. He did postdoctoral studies with Peter Cresswell at Duke and with Eric Long in the Laboratory of Immunogenetics in NIAID. In 1994 he joined the Experimental Immunology Branch of NCI, where he is now a senior investigator.

My research interest is in understanding basic mechanisms of protein trafficking in lymphocytes. Lymphocytes are major effectors of immunity, recognizing and ultimately eliminating foreign pathogens from the body.

My group has two distinct areas of interest: elucidating the basic mechanisms of intracellular granule exocytosis and studying the cell biology of antigen processing and presentation to T lymphocytes. We have approached our work using traditional techniques of molecular cell biology, and we are currently using confocal microscopy to address these issues in living cells.

Like all eukaryotic cells, lymphocytes rely on intracellular transport vesicles to shuttle membranes and cargo proteins from one compartment to another along the constitutive and regulated secretory pathways. These vesicles must dock and ultimately fuse with specific target membranes, and our goal is to understand the molecular mechanisms by which this specificity is achieved.

In neurons, a class of proteins known as SNAREs form a multiprotein complex that catalyzes the fusion of synaptic vesicles with the presynaptic plasma membrane, thereby allowing neurotransmitter to be released from intracellular stores into the synaptic cleft.

When I joined the Experimental Immunology Branch, the SNAREs that catalyze similar granule-plasma membrane fusion events in nonneuronal cells were not known. We therefore set out to identify the proteins necessary for secretion in immune cells. Using the yeast two-hybrid system, we isolated a ubiquitously expressed SNARE, termed SNAP-23, that mediates membrane-membrane fusion events in a wide variety of eukaryotic cells including lymphocytes.

SNAP-23 and other SNARE subunits behave as integral membrane proteins, yet they do not insert into membranes using the “traditional” co-translational

translocation machinery. We have shown that partial SNARE complexes containing SNAP-23 actually assemble in the cytosol and traffic to membranes post-translationally. Furthermore, we have cloned a novel kinase, termed SNARE-kinase, or SNAK, that phosphorylates cytosolic SNAP-23 and promotes assembly of SNARE complexes. Our current

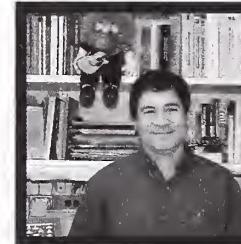
focus is on whether stimulating exocytosis in secretory cells alters SNARE complex assembly and whether regulated assembly-disassembly of SNAREs is required for granule exocytosis in lymphocytes. We are examining exocytosis by video microscopy. This allows us to observe the behavior of individual fluorescent secretory

granules in real time.

I have also had a long-standing interest in the cell biology of antigen processing and presentation to T cells. During immune surveillance, foreign pathogens are engulfed and degraded by antigen-presenting cells (APCs). Peptide fragments of these antigens are then presented on the cell surface of the APCs for recognition by antigen-specific T lymphocytes. Most of our work has been examining the biosynthesis, assembly, and intracellular trafficking of peptide-binding major histocompatibility complex (MHC) class II molecules. For example, we have found that newly synthesized MHC class II molecules are phosphorylated by protein kinase C in human APCs. This phosphorylation regulates the kinetics of intracellular transport of the class II molecules to endocytic peptide-loading compartments.

We have recently become very interested in the behavior of class II molecules on the surface of APCs. We have identified a novel role for plasma membrane lipid microdomains in concentrating the class II-peptide complexes necessary for T-cell activation. We are examining the components at the plasma membrane interface of APCs with T cells (the so-called “immunological synapse”). We are specifically interested in identifying the molecular signals that lead to the recruitment of T-cell-activating ligands (such as class II molecules) to this site.

It is likely that these two interests of the lab will converge, because some



Fran Pollner
Paul Roche

plasma membrane SNAREs themselves reside in lipid microdomains and may play a role in the targeting of intracellular class II-peptide complexes to specific regions of the plasma membrane. Although both SNARE function in protein traffic and the cell biology of T-cell activation are areas of intense research, more questions are left unanswered than answered, keeping our interest and excitement as high as ever.

Alexander Wilson received his doctoral degree in medical genetics from Indiana University, Indianapolis, in 1980. His postdoctoral training was in statistical genetics in the Department of Biometry and Genetics at the Louisiana State University Medical Center, New Orleans, where he rose to the rank of full professor in 1993 before joining NIH in 1995. He is currently a senior investigator and head of the Genometrics Section in the NHGRI Inherited Disease Research Branch and an adjunct full professor in the Department of Epidemiology at the Johns Hopkins University School of Public Health in Baltimore.

During the past 20 years, my research efforts have focused on using sophisticated statistical methods to identify genetic effects that may be responsible for phenotypic variation in quantitative traits.

My theoretical and methodological

work has focused on developing new methodologies to identify genetic effects and, using computer simulation, investigating the statistical properties of methods of genetic analysis for quantitative traits. I'm probably best known for developing a theoretical method that can be used to adjust for the effects of identified genetic loci, so that modifier loci can subsequently be identified. Before coming to NIH, I was one of the principal designers of the Statistical Analysis for Genetic Epidemiology (S.A.G.E.) software package, one of the most widely used statistical packages for the genetic analysis of family data.

Since coming to NIH in 1995, I've helped to establish the joint NIH/Johns Hopkins University Center for Inherited Disease Research (CIDR) in Baltimore and have authored or coauthored proposals to obtain over 650,000 genotypes from CIDR for studies searching for genetic loci involved in the phenotypic variation of scoliosis, obesity, cranio-lenticulo-sutural dysplasia, and hypertension.

Most recently, my work has focused on developing alternative methods for multipoint linkage analysis. Lynn Goldin of NCI and I have developed a method

based on moving averages to incorporate information from neighboring markers. And, Alexa Sorant, also of NHGRI, and I have proposed a method that uses composite markers derived from biallelic single-nucleotide polymorphic (SNP) markers.

We've shown that single-locus and multilocus marker systems are mathematically equivalent under certain critical assumptions and that with the appropriate statistical methods, composite markers based on SNP markers for linkage analysis can be nearly as informative as the traditional short tandem repeat markers.

My work in the future will continue to focus on the identification of genetic loci for quantitative traits such as hypertension and hypercalciuria, as well as on the development of statistical methods that can be used to tease the genetic effects out of these complex disorders. ■



Alexander Wilson

OOPS

Visitors to the NIDA molecular neuro-psychiatry labs headed by Jean Lud Cadet should go to the 3rd floor of the Johns Hopkins Bayview campus building in Baltimore. ■

National Institutes of Mental Help!

DENT



CALL FOR CATALYTIC REACTIONS

In this issue, we are asking for your reactions in four areas: health disparities research; training in the responsible conduct of research, advice for a new NIH director, and RNA-i.

Send your responses on these topics or your comments on other intramural research concerns to us via e-mail:
<catalyst@nih.gov>; fax: 402-4303; or mail: Building 2, Room 2W23.

In Future Issues...

- Proteomics
- Neuroscience Center
- The Odyssey Of a Teacher

- 1) What do you see as key areas of emphasis for the new Center for Research on Minority Health and Health Disparities or the NIH Academy in the years ahead? Do you have any suggestions about how to encourage bench and clinical intramural researchers to address health disparities questions? Do you think some adjustments are warranted in your own research agenda? Why or why not?
- 2) What can NIH do to maximize the effectiveness of training in the "responsible conduct of research"? Are you eager to receive this training?
- 3) What do you project will be the major challenges facing a new NIH director? What do you think should be the priorities of the person who will assume NIH leadership? What advice would you give a new director—or the incoming HHS secretary?

- 4) The *Catalyst* is contemplating an article on RNA-i (use of inhibiting RNA to selectively silence genes). Are you using this technique? In what organism and with what genes?

The NIH Catalyst is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 2, Room 2W23, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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